IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: John A. Lowe :

Examiner:Cybille Delacroix-Muirheid

APPLICATION NO.:09/007,268 :

Group Art Unit:1614

FILING DATE:January 14, 1998 :

TITLE: Fluoroalkoxybenzylamino Derivatives of Nitrogen Containg Heterocycles :

Commissioner for Patents
Washington, D.C. 20231

Sir:

Submission of Missing Page of Specification

On January 16, 2003, Applicants mailed an Amendment which should place the application in condition for allowance. An audit of the file, however, indicates that page 37 of the Specification was not included when the application was filed. A replacement copy of page 37 is submitted herewith. Submission is proper since there has been continuous copendency with prior applications (the immediate parent 08/167,881 is now a patent and copendency existed when the patent issued), and the parent is the U.S. national stage of PCT/US92/03571. The missing text corresponds to the bottom half of page 35 and the top half of page 36 of the PCT (a copy of the PCT pages is also provided in marked-up form. The examiner is welcome to contact the undersigned with any questions.

Respectfully submitted,

Date: 3/4/03

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^{1}H NMR (δ, $CDCl_3$): 1.27 (m, 1H), 1.4-1.8 (m, 2H), 1.90 (m, 1H), 2.05 (m, 1H), 2.63 (m, 1H), 2.78 (m, 2H), 2.88 (m, 1H), 3.19 (m, 1H), 3.45 (AB_q, J_{AB}=13.5, $\Delta\nu$=105.5, 2H), 3.72 (dd, J=8, 12, 1H), 4.43 (d, J=12, 1H), 6.31 (t, J=74 (H-F), 1H), 6.55 and 7.0-7.4 (m, 14H).

^{13}C-NMR ($CDCl_3$): 20.0, 24.9, 25.4, 42.0, 45.8, 49.4, 49.5, 55.0, 61.8, 116.3, 119.0, 125.4, 126.0, 126.5, 127.5, 127.8, 127.9, 128.0, 128.4, 128.5, 128.6, 129.1, 129.2, 130.0, 131.6, 143.2, 145.2, 149.3.

IR (cm^{-1}, neat): 2940 (C-H), 1599 (C=C).

MS (%): 449 (<1, parent+1), 291 (51), 281 (100), 84 (66), 49 (69).

Anal. Calc'd for $C_{28}H_{30}F_2N_2O$: C 74.98, H 6.74, N 6.25. Found: C 74.72, H 6.70, N 6.23.

EXAMPLE 2

(2S,3S)-N-(2-Methoxy-5-trifluoromethoxyphenyl)methyl-2-diphenylmethyl-1-azabicyclo[2.2.2]octane-3-amine methanesulfonic acid salt

The title compound was prepared in a manner similar to the procedure described in Example 1, by replacing 2-(difluoromethoxy)benzaldehyde with 2-methoxy-5-trifluoromethoxybenzaldehyde in Step B.

M.p. 135°C.

^{1}H NMR ($CDCl_3$) δ 1.8-2.3 (m, 2H), 2.2-2.8 (m, 6H), 2.66 (s, 6H), 3.56 (s, 3H), 3.3-3.7 (m, 3H), 3.90 (m, 3H), 4.16 (m, 2H), 5.06 (m, 1H), 5.20 (br, 1H), 5.50 (m, 1H), 5.60 (br, 1H), 6.77 (d, 1H, J=9.2), 7.02 (m, 1H), 7.2-7.8 (m, 11H), 8.00 (br, 1H), 10.8 (br, 1H).

IR (cm^{-1}, KBr): 3180, 3140, 3000, 1500, 1200, 1062, 782.

EXAMPLE 3

(2S,3S)-2-Phenyl-3-[2-(2,2,2-trifluoroethoxy)benzyl]-aminopiperidine hydrochloride

A. **2-(2,2,2-Trifluoroethoxy)benzaldehyde**

Under a nitrogen atmosphere in a round-bottom flask equipped with a reflux condenser were plac d 0.2 g (1 mmol)

B. 2-(Diphenylmethyl)-N-((2-difluoromethoxy)-phenyl)methyl-1-azabicyclo[2.2.2]octan-3-amine

To a 25 mL round-bottomed flask equipped with a nitrogen inlet were added 500 mg (1.71 mmol) 2-diphenylmethyl-1-azabicyclo[2.2.2]octan-3-amine (prepared according to the method of Warawa, et al., J. Med. Chem., 17, 497 (1974)), 8.5 mL methanol, 383 mg (2.23 mmol) 2-(difluoromethoxy)-benzaldehyde, and 216 mg (3.42 mmol) sodium cyanoborohydride. The reaction was stirred at room temperature for 30 hours, partitioned between ethyl acetate and water. The organic layer was separated, washed with brine, dried over sodium sulfate, and evaporated. To remove the last traces of unreacted amine, the mixture was treated with sodium triacetoxyborohydride in acetic acid at room temperature for 16 hours, then worked up with aqueous sodium hydroxide and methylene chloride. The residue was crystallized from isopropanol to afford a white solid, m.p. 144-147°C, 206 mg (27%).

^{1}H NMR (δ, $CDCl_3$): 1.27 (m, 1H), 1.4-1.8 (m, 2H), 1.90 (m, 1H), 2.05 (m, 1H), 2.63 (m, 1H), 2.78 (m, 2H), 2.88 (m, 1H), 3.19 (m, 1H), 3.45 (AB_q, J_{AB}=13.5, $\Delta\nu$=105.5, 2H), 3.72 (dd, J=8, 12, 1H), 4.43 (d, J=12, 1H), 6.31 (t, J=74 (H-F), 1H), 6.55 and 7.0-7.4 (m, 14H).

^{13}C-NMR ($CDCl_3$): 20.0, 24.9, 25.4, 42.0, 45.8, 49.4, 49.5, 55.0, 61.8, 116.3, 119.0, 125.4, 126.0, 126.5, 127.5, 127.8, 127.9, 128.0, 128.4, 128.5, 128.6, 129.1, 129.2, 130.0, 131.6, 143.2, 145.2, 149.3.

IR (cm^{-1}, neat): 2940 (C-H), 1599 (C=C).

MS (%): 449 (<1, parent+1), 291 (51), 281 (100), 84 (66), 49 (69).

Anal. Calc'd for $C_{28}H_{30}F_2N_2O$: C 74.98, H 6.74, N 6.25. Found: C 74.72, H 6.70, N 6.23.

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(2S,3S)-N-(2-Methoxy-5-trifluoromethoxyphenyl)methyl-2-diphenylmethyl-1-azabicyclo[2,2,2]octane-3-amine methanesulfonic acid salt

The title compound was prepared in a manner similar to the procedure described in Example 1, by replacing 2-(difluoromethoxy)benzaldehyde with 2-methoxy-5-trifluoromethoxybenzaldehyde in Step B.

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IR (cm^{-1}, KBr): 3180, 3140, 3000, 1500, 1200, 1062, 782.

EXAMPLE 3

(2S,3S)-2-Phenyl-3-[2-(2,2,2-trifluoroethoxy)benzyl]-aminopiperidine hydrochloride

A. 2-(2,2,2-Trifluoroethoxy)benzaldehyde

Under a nitrogen atmosphere in a round-bottom flask equipped with a reflux condenser were placed 0.2 g (1 mmol) of 2-(2,2,2-trifluoroethoxy)benzonitrile (J. Org. Chem., 377 (1983)) and 5 mL of formic acid. To this solution was added ca. 0.2 g of Raney nickel, and the mixture was heated at reflux for 90 minutes. The mixture was filtered through diatomaceous earth, and the filter cake was rinsed with water and chloroform ($CHCl_3$). The layers were separated, and the aqueous phase was extracted with three portions of chloroform. The combined organic fractions were washed with saturated aqueous sodium bicarbonate and water, dried over sodium sulfate (Na_2SO_4) and concentrated (rotary evaporator) to obtain 176 mg of the title compound as a yellow solid, m.p. 33-34°C.